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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/606,159	JANJIC ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) *1-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Claims 1-6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on February 16, 2006.

Claim Rejections - 35 USC § 103

Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gold et al. in view of Tullis and Ferns et al. (all of record).

Claim 7 is directed to a method of improving the pharmacokinetic properties of a PDGF nucleic acid ligand by covalently linking the ligand to either a lipophilic compound or a non-immunogenic, high molecular weight compound and administering the complex to a patient. Claim 8 is directed to a method of targeting a therapeutic or diagnostic agent to a particular predetermined biological target in a patient by covalently linking the agent to a complex of a PDGF nucleic acid ligand and a lipophilic compound or a non-immunogenic, high molecular weight compound and administering the complex to a patient.

Gold et al. teach a method of identifying nucleic acid ligands by a process of *in vitro* selection and amplification. Targets for nucleic acid ligands include growth

factors. Nucleic acid ligands are also referred to as nucleic acid antibodies and Gold et al. teach that nucleic acid ligands can be employed in diagnostics in a manner similar to conventional antibody-based diagnostics. Gold et al. also teach that nucleic acid ligands have therapeutic uses as sequestering agents, drug delivery vehicles and modifiers of hormone action. Gold et al. do not teach conjugation of a nucleic acid ligand to a non-immunogenic, high molecular weight compound or a lipophilic compound.

Tullis teaches nucleic acid conjugates comprising an antisense conjugated to a solubility modifying moiety that may be hydrophobic and imparts amphiphilic character to the final product. At page 7 solubility modifying moieties are taught as including polyethylene glycol as well as lipophilic compounds such as palmitate, distearylglyceride and cholesteryl. Tullis teaches that the conjugates of the invention find use in therapeutics wherein the amphiphilic nature of the conjugate aids in transport across the cellular membrane and that the conjugates improve other pharmacokinetic properties such as nuclease resistance.

Ferns et al. teach that PDGF is involved in the accumulation of smooth muscle cells that is the main cause of restenosis after angioplasty. Ferns et al. further teach that administration of PDGF antibodies to rats before and after balloon catheter deendothelialization, a model of angioplasty induced restenosis, reduced the amount of smooth muscle cell accumulation observed. Ferns et al. teach that their findings suggest possible approaches for prevention of restenosis following angioplasty.

It would have been obvious to one of ordinary skill in the art at the time of invention to improve the pharmacokinetic properties of a nucleic acid ligand as taught by Gold et al. by conjugating the ligand to a solubility modifying moiety such as PEG or cholesterol as taught by Tullis. It would have been further obvious to one of ordinary skill to make nucleic acid ligands that are targeted to PDGF. Tullis provides a motivation to make conjugates of nucleic acids and solubility modifying moieties, teaching that such conjugates increase pharmacokinetic properties such as cellular uptake and nuclease resistance. It would have further been obvious to use a nucleic acid ligand complex to deliver a therapeutic or diagnostic agent because Gold et al. explicitly suggest drug delivery vehicles are one of the utilities of nucleic acid ligands. Ferns et al. provide a motivation to target PDGF, teaching that PDGF is involved in the accumulation of smooth muscle cells that is the main cause of restenosis and that inhibition of PDGF reduces restenosis. One of ordinary skill in the art would have had a reasonable expectation of success in producing a nucleic acid ligand to PDGF because Gold et al. teach a method of isolating nucleic acid ligands to any target molecule and state that growth factors are a desired target. One of ordinary skill in the art would have had a reasonable expectation of success in making a conjugate of solubility modifying moiety and a nucleic acid ligand because Tullis teaches that such oligonucleotide conjugates are made using routine synthesis methods.

Thus, the invention of claims 7 and 8 would have been obvious, as a whole, at the time of invention.

Response to arguments

Applicants traverse the rejection of record by arguing there is not a reasonable expectation of success in combining the references, arguing that nucleic acid ligands are not equivalent to the nucleic acids described by Tullis, noting that nucleic acid ligands are characterized by exhibiting high specificity binding to a given target molecule. Applicants argue that for nucleic acid ligands, the three dimensional structure is of key importance and submit that the teachings of Gold et al. do not provide a reasonable expectation that a functional PDGF nucleic acid ligand conjugate will be obtained. Applicants further note that the specification defines nucleic acid ligands as a non-naturally occurring nucleic acid having a desirable action (including binding) on a target and that the claimed invention, complexes of such nucleic acid ligands, are functional nucleic acid ligands. Applicants assert that the cited references do not contain a sufficient teaching of how to obtain this desired result, or that this claimed result would be obtained if certain directions were pursued. Applicants conclude that the art cited, at most, "piques the scientist's curiosity."

Applicants' conclusions that the cited art "piques the scientist's curiosity" and the inclusion of quotations from court cases regarding whether "obvious to try" is a proper standard for determining obviousness appear to indicate the belief that this standard has been applied in the pending rejection. This is not the case; the rationale for combining the cited references is based on motivation and reasonable expectation of success, not whether it would be obvious to try to combine the references.

Each of applicants' arguments rests on the proposition that the nucleic acid ligands obtained by the combination of the cited references would have to maintain their function, i.e. be able to bind a target, and that the person of ordinary skill in the art would not be able to produce conjugates of nucleic acid ligands with the reasonable expectation that a conjugated ligand would remain functional.

Applicants submit that the teachings of Gold et al. do not provide a reasonable expectation that a functional PDGF nucleic acid ligand conjugate will be obtained, but provide no specific reasons why Gold et al.'s teachings do not provide this reasonable expectation. However, it is noted that the rejection is not based on the teachings of Gold et al. alone.

The examiner acknowledges that nucleic acid ligands have certain characteristics different from those of the antisense sequences used in the Tullis reference, however, the person of ordinary skill in the art recognizes based on the teachings of Gold et al. that the usefulness of a nucleic acid ligand rests on its affinity for a target and that in order for the claimed method to be useful the nucleic acid ligand would have to maintain its affinity.

Applicants assert the possible disruption of three dimensional structure of the nucleic acid ligand with the addition of a non-immunogenic, high molecular weight compound or lipophilic compound is a parameter that may have precluded any successful result and asserts that this possible disruption mandates more than routine testing to determine if the three dimensional structure of an aptamer has been affected by the conjugation. Applicants conclude that the cited references do not teach how to

obtain the desired result of maintaining binding affinity or that this result would be obtained if certain directions were pursued.

Applicants' arguments are not persuasive because applicants assert that more than routine testing would be required to determine if an aptamer's three dimensional structure is maintained but provides no reasons why such testing would not be routine for one of ordinary skill in the art. The examiner recognizes that it is impossible to determine *a priori* whether a particular conjugate will affect target affinity of a nucleic acid ligand, but such a determination is not required to conclude there is a reasonable expectation of success in making conjugates of nucleic acid ligands that substantially maintain their binding affinity. in view of the advanced state of the art regarding conjugation of molecules to nucleic acids and the recognition by those in the art that conjugates can be produced by attachment at numerous points within a nucleic acid using routine synthetic methods, determining that a conjugate maintains its affinity is routine and predictable. If production of any particular conjugate is observed to abolish binding affinity, one of ordinary skill would immediately recognize how this problem is to be solved; therefore one of ordinary skill would have a reasonable expectation that conjugates of nucleic acid ligands that maintain their binding affinity can be produced using only routine synthetic methods.

Applicants additionally argue that the previously cited Veronese publication provides additional evidence that there was not reasonable expectation of success by illustrating that it was not known in the art that the present disclosure could be

successful. This argument cannot be addressed because applicants do not specify what additional evidence is provided by the Veronese publication.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Tracy Vivlemore/
Examiner
Art Unit 1635

TV
February 22, 2008